

Ophthalmology Update

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Figure. Center-involving diabetic macular edema.

Patients May Receive Cataract Surgery if Diabetic Macular Edema is Managed Pre- and Post-Surgery

Diabetic retinopathy is the leading cause of preventable blindness among working-aged adults. It affects more than 33% of patients with diabetes mellitus. Among these patients, diabetic macular edema (DME) remains a leading cause of visual impairment. “Patients with diabetes mellitus are also more likely to develop cataracts and tend to develop them at a younger age compared with other patients. When patients with DME develop visually significant cataracts, a relevant question is whether cataract surgery will worsen the diabetic eye disease,” says Sophie J. Bakri, M.D., chair of Ophthalmology at Mayo Clinic in Rochester, Minnesota.

To investigate that question, Dr. Bakri and fellow researchers performed a retrospective chart review of all patients with active DME who received treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections before and after cataract surgery at Mayo Clinic in Rochester, Minnesota, from Jan. 1, 2012, through Dec. 31, 2017. The use of intravitreal anti-VEGF agents is an established treatment for DME.

Inclusion criteria included diagnosis of DME in the operative eye (Figure) and an intravitreal anti-VEGF injection in the operative eye within the six months prior to surgery. In 32 patients with active DME, 40 eyes were actively being managed with

ipsilateral intravitreal anti-VEGF injections and were treated with cataract surgery during the five-year study period; 37 eyes of 30 patients were included in the study.

Outcome measures included the development of subretinal or intraretinal fluid in the six months following surgery, timing and number of injections, best corrected visual acuity, and central subfield thickness (CST) on optical coherence tomography (OCT).

“Patients were typically managed with an initial series of 2 to 4 injections at a defined interval (typically every four weeks) and were reevaluated with repeat OCT imaging after the completion of the initial series,” notes Dr. Bakri. “Based on the imaging findings and clinical exam, the interval between injections was increased (improved fluid findings on OCT), remained unchanged (stable OCT findings) or was decreased if greater than four weeks (with new fluid findings on OCT).”

WORSENING DME DOES NOT AFFECT VISUAL ACUITY

The researchers found a significant improvement between pre- and postoperative best corrected visual acuity when comparing all eyes ($P < 0.0001$) and no significant difference in CST before and after surgery ($P > 0.05$). Preoperative OCT found fluid in 30 eyes (81.1%).



Sophie J. Bakri, M.D.

Dr. Bakri notes: “Following surgery there was a statistically significant improvement in mean visual acuity without a statistically significant increase in retinal thickness; however, nearly 50% of eyes had some worsening of DME following surgery (although not statistically significant). The increased DME did not appear to affect visual outcomes, and eyes with worse DME still had a significant improvement in visual acuity. There was also no increase in the number of anti-VEGF injections postoperatively.

“Despite the active DME, cataract surgery in the eyes in our study was still successful, with improvement in vision and stable CST measurements. The success is likely owed to the active management with pre- and postoperative anti-VEGF therapy. Therefore,

patients with active DME and visually significant cataract can consider cataract surgery while maintaining an effective perioperative intravitreal anti-VEGF regimen when needed — but those patients need to understand that the DME may worsen and perhaps need increased treatment.”

Study results were published in the *American Journal of Ophthalmology* in 2021.

FOR MORE INFORMATION

Starr MR, et al. Outcomes of patients with active diabetic macular edema at the time of cataract surgery managed with intravitreal anti-VEGF injections: Outcomes of cataract surgery in active DME patients. *American Journal of Ophthalmology*. 2021;229:194.

IPL-MGX Improves Dry Eye Symptoms More Than MGX Alone in Treating Ocular Rosacea With Dry Eye



Joanne F. Shen, M.D.

Dry eye disease is a common condition causing ocular discomfort, reduced visual acuity and impaired quality of life. Meibomian gland dysfunction is the most common cause of dry eye disease: Abnormal meibum obstructs meibomian glands and causes altered tear film, which can result in eye irritation, ocular surface disease, inflammation and bacterial overgrowth.

“When meibomian gland dysfunction is treated early, there is potential for the return of gland function. However, many of the current therapies only treat the symptoms of dry eye disease rather than addressing the underlying pathophysiology of meibomian gland dysfunction,” says Joanne F. Shen, M.D., chair of Ophthalmology at Mayo Clinic in Phoenix/Scottsdale, Arizona.

understood and the treatment is not widely available,” says Dr. Shen.

Dr. Shen and fellow researchers investigated the efficacy and mechanism of IPL in ocular rosacea with dry eye symptoms by evaluating symptoms and signs and analyzing tear film transforming growth factor-beta (TGF-β) and ocular microbiome changes in patients receiving IPL with MGX compared with MGX alone. Results were published in *Clinical Ophthalmology* in 2021.

For this pilot study, 20 patients with a greater than one-year history of ocular rosacea with meibomian gland dysfunction and dry eye disease were recruited from November 2017 through September 2018 and randomly assigned to receive either IPL-MGX or MGX. Patients were examined, treated and administered the Ocular Surface Disease Index survey every 4 to 6 weeks for four total treatments. Tear film and conjunctival samples were collected at first and last visits and analyzed for TGF-β concentration and 16s rRNA amplicon sequencing of ocular microbiome.

OCULAR SURFACE DISEASE INDEX SURVEY RESULTS

Mean baseline Ocular Surface Disease Index scoring was equivalent between the IPL-MGX and the MGX treatment groups (55.7 versus 43.5, P = 0.212). By the fourth visit,



Figure. Dharmendra (Dave) R. Patel, M.D., an ophthalmologist at Mayo Clinic in Phoenix/Scottsdale, Arizona, treats a patient with intense pulsed light.

Meibomian gland expression (MGX) is a relatively inexpensive and readily available treatment option that requires minimal equipment and has proved efficacious in patients with dry eye related to meibomian gland dysfunction. However, it is often painful and requires frequent treatment sessions. Intense pulsed light (IPL) combined with MGX is a recognized treatment for ocular rosacea and meibomian gland disease with dry eye symptoms (Figure), but “despite the growing acceptance of IPL in ophthalmology, the mechanism by which it improves dry eye symptoms is not fully

scores were significantly improved from baseline in the IPL-MGX treatment group compared with the group that received MGX alone ($P = 0.030$).

The number of meibomian glands yielding liquid secretions increased from baseline to visit 4 in both groups. The increase was greater in the IPL-MGX group, though not different enough to achieve statistical significance in this small cohort.

Dermatology literature has reported elevation in TGF- β 1 in patients with back acne treated with IPL, so an association was investigated in the patients with ocular rosacea. However, there was no significant difference in mean TGF- β 1, TGF- β 2 or TGF- β 3 concentration after IPL-MGX ($P = 0.385, 0.709$ and 0.948 , respectively). Ocular microbiome was examined, but though quantities of clostridium, klebsiella, brevibacterium, lactobacillus, neisseria, streptococcus, corynebacterium, butyricoccus and actinomyces were significantly reduced from baseline in both

groups, there was no significant difference between the two treatment groups.

Dr. Shen concludes: “Refractory dry eye symptoms can be extremely debilitating. There is an array of treatments offered to patients with dry eye, many of which are not covered by insurance and lack any guarantee of improvement. Patients who have ocular rosacea and respond to doxycycline but are intolerant to this systemic treatment are good candidates for this out-of-pocket cost treatment. Patients with refractory red eyes from ocular rosacea also have responded well. Understanding the mechanism of IPL on dry eye from ocular rosacea will both enable providers to identify other patients as good candidates based on their individual traits and open the door to investigating additional therapeutic interventions.”

FOR MORE INFORMATION

Sagaser S, et al. Effects of intense pulsed light on tear film TGF- β and microbiome in ocular rosacea with dry eye. *Clinical Ophthalmology*. 2021;15:323.

Netarsudil Significantly Reduces Intraocular Pressure in Patients With Primary Open-Angle Glaucoma

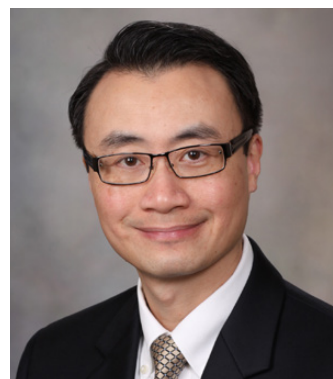
Intraocular pressure (IOP) reduction is key to controlling primary open-angle glaucoma (POAG), the second-leading cause of blindness worldwide (Figure, see page 4). “Elevated IOP resulting from increased resistance to aqueous humor outflow is a critical risk factor for POAG and is, thus far, the only causative factor that can be modified,” says Arthur J. Sit, M.D., M.S., Ophthalmology, at Mayo Clinic in Rochester, Minnesota. “Pharmacological therapies to reduce elevated IOP are the most common options for controlling or delaying disease progression.”

Most common medications used for patients with POAG or ocular hypertension (OHT) lower IOP by increasing uveoscleral drainage or by decreasing production of aqueous humor. However, few medications target the site of abnormality in POAG and OHT: the trabecular meshwork. “Unfortunately, no IOP-lowering treatment is effective for all patients, and previous medications that targeted the trabecular meshwork either worked indirectly or were poorly tolerated,” says Dr. Sit.

Netarsudil, a Rho kinase and norepinephrine transporter inhibitor, was approved by the U.S. Food and Drug Administration in 2017 for the reduction of elevated IOP in patients with POAG or OHT. While netarsudil was developed to act on the trabecular meshwork, the mechanism of action for IOP reduction by netarsudil had not previously been investigated in patients with POAG or OHT.

To understand the mechanism of action of netarsudil, Dr. Sit and fellow researchers measured changes in aqueous humor dynamics including trabecular outflow facility, episcleral venous pressure (EVP) and IOP in patients with POAG or OHT following treatment for seven days with netarsudil ophthalmic solution 0.02%. Their phase 2 study was published in the *American Journal of Ophthalmology* in 2021. The study’s modified intent-to-treat population ($n = 18$) included all randomized patients who met the following criteria:

- At least one dose of study medication was administered.



Arthur J. Sit, M.D., M.S.

- All baseline measurements and post-baseline measurements for outflow facility were collected.
- Mean diurnal IOP was at least 2 mm Hg lower than baseline mean diurnal IOP in the same eye treated with netarsudil (responders).

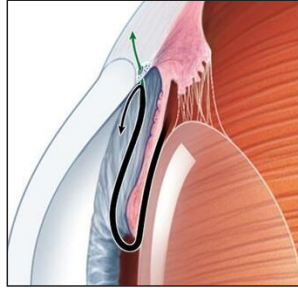


Figure. Intraocular pressure in primary open-angle glaucoma.

Patients attended three study visits, beginning with a screening visit (visit 1) conducted up to six weeks prior to the qualification baseline visit (visit 2 on day 1). Patients using existing glaucoma medications were washed out over 1 to 6 weeks depending on the medication. Those who passed the qualification visit then instilled netarsudil 0.02% into one eye and vehicle into the contralateral eye each morning on days 2 through 7. On day 8 (visit 3), the final treatment was administered at 8 a.m., followed by post-treatment assessment.

RESULTS

The primary efficacy endpoint of the study was change in mean diurnal trabecular outflow facility (the average of facility measurements at 1 p.m. and 4 p.m.) on day 8 compared with that on day 1 (baseline). Results included the following:

- Mean diurnal outflow facility increased 0.039 $\mu\text{L}/\text{min}/\text{mm Hg}$ versus 0.007 $\mu\text{L}/\text{min}/\text{mm Hg}$ from baseline in the netarsudil- and the vehicle-treated groups, respectively ($P < 0.001$ versus baseline for

netarsudil), a treatment difference of 0.03 $\mu\text{L}/\text{min}/\text{mm Hg}$ ($P \leq 0.001$).

- Mean diurnal IOP change from baseline at day 8 was -4.52 mm Hg for netarsudil versus -0.98 mm Hg for vehicle, a treatment difference of -3.54 mm Hg ($P < 0.0001$).
- Mean diurnal EVP change from baseline was -0.79 mm Hg in the netarsudil-treated group versus 0.10 mm Hg for vehicle, a treatment difference of -0.89 mm Hg ($P < 0.001$).

Dr. Sit concludes: “In this study, once-daily dosages of netarsudil ophthalmic solution 0.02% for seven days lowered IOP by improving outflow facility and reducing EVP. Trabecular outflow facility increased by approximately 35% from baseline and 25% versus vehicle-treated controls with netarsudil treatment. The change from baseline in trabecular outflow facility accounts for approximately 80% of the mean change in IOP in the treatment group, which decreased nearly 20% after seven days of once-daily netarsudil treatment.”

FOR MORE INFORMATION

Sit AJ, et al. Netarsudil improves trabecular outflow facility in patients with primary open angle glaucoma or ocular hypertension: A phase 2 study. *American Journal of Ophthalmology*. 2021;226:262.

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Ophthalmology Update

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Cover Image

Human multicolored iris of the eye animation concept. Credit: CG Alex

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